REMARKS

Status of the Claims

Claims 12-28 are pending. Claims 14-16 and 19 are withdrawn.

Claim 26 is amended and claims 27 and 28 are new. Support for the amendment and new claims can be found in the specification (as published in US/2004/0146909A1) in paragraphs 188 and 193, for example.

Upon entry of the amendment, claims 12, 13, 17, 18 and 20-28 are under consideration.

Claim Rejections under 35 USC 112

The Examiner has rejected claim 26 under 35 USC 112, first paragraph as allegedly failing to comply with the written description requirement for presenting new matter. The Examiner on page 3 of the office action of November 27, 2009, states that claim 26 is not supported by the specification since "the claim does not require that one of different ETMS is a transition metal complex. Furthermore, in applicants' remarks filed July 14, 2009, applicants do not indicate which part in the specification supports such claim limitation recited in claim 26."

Without admitting to the propriety of the rejection, Applicants have amended claim 26 such that "at least one of the plurality of different ETMs comprises a transition metal complex." Furthermore, Applicants note that in paragraph 225 (emphasis added), the specification teaches that

> [i]n addition, substituent groups on an ETM, particularly metallocenes such as ferrocene, may be added to **alter the redox properties** of the ETM. Thus, for example, in some embodiments, as is more fully described below, **it may be desirable to have different ETMs attached** in different ways (i.e. base or ribose attachment), on different probes, or for different purposes (for example, calibration or as an internal standard). Thus, the addition of substituent groups on the metallocene may **allow two different ETMs to be distinguished.**

As previously argued, different ETMs having different potentials result in differential responses to applied energy, allowing the different ETMs to be detected.

In view of the above, Applicants submit that the claims are fully compliant with the written description requirement. Withdrawal of the rejection is respectfully requested.

The Examiner has rejected claims 12, 13, 17, 18 and 20-26 as allegedly indefinite. With respect to claim 25, the Examiner states that "it is unclear why an output waveform generated from an input waveform can indicate the presence of said target analyte and

cannot indicate the presence of said capture binding ligand." Applicants submit, however, that it might be possible in some embodiments to detect electron transfer due to the presence of an ETM associated with a capture binding ligand, but such electron transfer can be distinguished from electron transfer due to the presence of a target analyte in an assay complex.

According to the specification, detecting the presence of a target analyte can be accomplished in at least two ways. First, according to paragraph 25 (emphasis added),

> [i]n a preferred embodiment, detection of an ETM is based on electron transfer through the stacked π-orbitals of **double stranded nucleic acid**. This basic mechanism is described in U.S. Pat. Nos. 5,591,578, 5,770,369, 5,705,348, and PCT US97/20014 and is termed "mechanism-1" herein. Briefly, previous work has shown that **electron transfer can proceed rapidly through the stacked π-orbitals of double stranded nucleic acid, and significantly more slowly through single-stranded nucleic acid**. Accordingly, this can serve as the basis of an assay. Thus, by adding ETMs (either covalently to one of the strands or non-covalently to the hybridization complex through the use of hybridization indicators, described below) to a nucleic acid that is attached to a detection electrode via a conductive oligomer, electron transfer between the ETM and the electrode, through the nucleic acid and conductive oligomer, may be detected.

Thus, in some embodiments, an ETM can be associated with (i.e., bound to) a capture binding ligand, but the target analyte is not detected unless it is present to form an assay complex such that electron transfer can proceed rapidly through π-orbitals of double stranded nucleic acid, as compared to the much slower rate that occurs through single stranded nucleic acid. In these embodiments, it is the **differential rate of electron transfer** between double and single stranded nucleic acid that allows the target analyte to be detected.

In other embodiments, a different mechanism of electron transfer occurs. Paragraph 27 of the specification, emphasis added, teaches that

> [a]lternatively, the presence or absence of ETMs can be directly detected on a surface of a monolayer. **That is, the electrons from the ETMs need not travel through the stacked [π** (see specification as filed on page 6, line 2)] **orbitals in order to generate a signal.** As above, in this embodiment, the detection electrode preferably comprises a self-assembled monolayer (SAM) that serves to shield the electrode from redox-active species in the sample. **In this embodiment, the presence of ETMs on the surface of a SAM, that has been formulated to comprise slight "defects" (sometimes referred to herein as "microconduits", "nanoconduits" or "electroconduits") can be directly detected.** This basic idea is termed "mechanism-2" herein. Essentially, the electroconduits allow particular ETMs access to the surface. Without being bound by theory, it should be noted

> that the configuration of the electroconduit depends in part on the ETM chosen. For example, the use of relatively hydrophobic ETMs allows the use of hydrophobic electroconduit forming species, which effectively exclude hydrophilic or charged ETMs. Similarly, the use of more hydrophilic or charged species in the SAM may serve to exclude hydrophobic ETMs.

Accordingly, in some embodiments, an ETM can be associated with (i.e., bound to) the target analyte, for example, which can be detected upon formation of an assay complex that places the ETM in proximity to the electrode.

For the Examiner's reference, illustrations of different embodiments of "mechanism-1" and "mechanism-2" can be found in International Application No. PCT/US99/01705 (cited in paragraph 24; published as WO/1999/037819), Figs. 30 and 16 respectively.

According to the above discussion, it is upon formation of an assay complex comprising a target analyte that electron transfer can occur through at least either of the two mechanisms described above, thus indicating the presence of the target analyte. Any electron transfer that is due to association of an ETM with a capture binding ligand can be distinguished.

Also, the Examiner states that claim 25 is "vague and indefinite because it is unclear that the analyzing the output waveform using peak recognition of what." Applicants note that it is understood in the art that "peak recognition" refers to the **recognition of peaks** in a signal or output waveform (e.g., whether represented in the time or frequency domain). "Peak recognition" also known as "peak detection" in the art can be performed using various algorithms known in the art. See, e.g., paragraph 458 and also http://zone.ni.com/devzone/cda/tut/p/id/3770#toc1 (attached as Exhibit A). As described by the specification in paragraph 21, the present application provides techniques that can be used to increase the signal-to-noise ratio in target analyte detection assays. One technique involves the use of data processing, that is, techniques used on the "output" signals to maximize or identify sample signal. Paragraph 21 teaches that examples of "output" techniques include background subtraction techniques, such as peak recognition. Paragraph 458 states that peak recognition can be achieved through various models, whether linear or nonlinear. Thus, a signal generated by the system can be analyzed using a variety of computational techniques in order to increase or identify sample signal against a background of noise that may be present under given experimental conditions. These computational techniques include "peak recognition", that is, recognition of peaks in some form of the signal. Thus, in view of the specification

and knowledge of one of skill in the art, the term "peak recognition" is clearly understood.

Finally, the Examiner states that claim 26 is indefinite for reasons similar to those indicated for claim 25. Specifically, the Examiner states that "[s]ince the claim does not indicate that a plurality of different ETMs only associates with a plurality of different target analytes and does not associate with said capture analyte, it is unclear why detecting said plurality of different ETMS can be used as a measure of the presence of said plurality of different target analytes and cannot used as a measure of the presence of said capture binding ligand in claim 25." Applicants believe that claim 26 is not indefinite for the same reasons explained above for claim 25. In summary, any electron transfer that is due to association of an ETM with a capture binding ligand can be distinguished from electron transfer due to an ETM associated with a target analyte.

In view of the above, it is believed that claims 25 and 26 are not indefinite. Withdrawal of the rejections is respectfully requested.

Double Patenting

The Examiner has rejected claims 12, 13, 17, 18 and 20-26 as allegedly unpatentable over claims 1-27 of US Patent 6,740,518 on the grounds of nonstatutory obviousness-type double patenting. Applicants respectfully request that this rejection be held in abeyance until patentable subject matter has been found notwithstanding any double patenting rejection.

Conclusion

In view of the foregoing, Applicants believe that the claims are in condition for allowance, and early notification thereof is requested. The Examiner is invited to call the undersigned if necessary to expedite prosecution of this application. Although Applicants do not believe that any additional fees are due, the Commissioner is authorized to charge any fees required or to credit any overpayment to Deposit Account No. 50-0310 (Docket No. 067456-5012-US02).

Respectfully submitted,

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